

# Priorities for Emergency Department Syncope Research

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**Study objectives:** There is limited evidence to guide the emergency department (ED) evaluation and management of syncope. The First International Workshop on Syncope Risk Stratification in the Emergency Department identified key research questions and methodological standards essential to advancing the science of ED-based syncope research.

**Methods:** We recruited a multinational panel of syncope experts. A preconference survey identified research priorities, which were refined during and after the conference through an iterative review process.

**Results:** There were 31 participants from 7 countries who represented 10 clinical and methodological specialties. High-priority research recommendations were organized around a conceptual model of ED decisionmaking for syncope, and they address definition, cohort selection, risk stratification, and management.

**Conclusion:** We convened a multispecialty group of syncope experts to identify the most pressing knowledge gaps and defined a high-priority research agenda to improve the care of patients with syncope in the ED. [Ann Emerg Med. 2014;64:649-655.]

A **podcast** for this article is available at [www.annemergmed.com](http://www.annemergmed.com).

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## INTRODUCTION

### Background and Importance

There is pervasive and persistent uncertainty about the optimal emergency department (ED) evaluation and management of syncope. Evidence from multiple countries suggests extensive practice variation, high costs, and questionable benefit associated with current approaches.<sup>1-23</sup> For example, syncope accounts for an annual 740,000 ED visits and \$2.4 billion in health facility costs in the United States,<sup>19</sup> and hospitalization does not clearly improve outcomes<sup>21</sup> or diagnostic yield.<sup>10</sup> Professional society guidelines offer differing recommendations on testing algorithms and diagnostic admissions<sup>24-30</sup> and rely heavily on expert consensus.

Despite worldwide interest in developing ED syncope care algorithms<sup>4,8,11,31-38</sup>, a rigorous evidence base remains underdeveloped.<sup>39</sup> Fragmentation of research efforts across different clinical specialties and countries represents a major barrier to advancing the science of ED syncope care. Furthermore, major variations in patient populations, outcome measures, outcome time frames, recorded risk factors, and analytic approaches seriously limit attempts to synthesize the existing literature.<sup>40</sup>

## GOALS OF THIS CONFERENCE

The overall objective of this study is to improve the quality of ED syncope research to support clinical management decisions. We organized a multinational and multispecialty workshop of syncope experts to develop a research agenda for the ED evaluation and management of syncope. There were 2 major goals: identify high-priority research questions for investigators and potential funders, and develop methodological standards for ED syncope research.

## MATERIALS AND METHODS

### Participant Recruitment

We organized this multidisciplinary research consensus conference, the first of its kind, in Gargnano, Italy, on September 26 to 27, 2013. We identified 40 potential participants according to previous published research on syncope or participation in professional society guidelines (eg, European Society of Cardiology,<sup>25</sup> American College of Emergency Physicians,<sup>41</sup> Canadian Cardiovascular Society,<sup>29</sup> American College of Physicians<sup>27</sup>) on the management of syncope. Participants represented a wide range of clinical and methodological specialties, with the unifying theme of clinical and research

expertise in the management of syncope. We explicitly sought the expertise of non-ED-based physicians, including electrophysiologists, cardiologists, neurologists, geriatricians, and occupational health clinicians, for their perspectives on acute management, transitions from ED to non-ED settings of care, and work and driving recommendations after acute hospital evaluation. Two months before the conference, all participants were invited to complete an Internet-based survey to identify top research priorities for the ED evaluation and management of syncope. Potential agenda topics were ranked on a 0- to 5-point Likert scale (Figure E1, available online at <http://www.annemergmed.com>). All but 2 of the participants completed the survey. Responses to these survey questions guided the development of conference sessions. Activities of this meeting were exempt from local institutional review board review.

### Conference Activities and Research Agenda Development

Consensus conference included 4 sessions, 1 on each of the following topics: clinical decision rules, defining risk thresholds, patient management, and proposals for new studies. Each session included formal presentations by participants, as well as moderated group discussions. Each session aimed to identify important knowledge gaps, explore areas of disagreement, and create a group consensus for research priorities. Session leaders kept written notes of all discussions. All attendees participated in each of the sessions.

A scientific committee of 10 members (B.C.S., G. Constantino, F.B., G. Casazza, D.M., J.Q., M.R., R.S., V.T., R.F.) synthesized the conference discussions into a consensus document, which was subsequently reviewed and endorsed by all conference participants. This document has been endorsed by the following organizations: the Gruppo Italiano Multidisciplinare per lo Studio della Sincope (Italian Multidisciplinary Group for Syncope Evaluation), the Società Italiana di Medicina d'Emergenza–Urgenza (Italian Society of Emergency Medicine), and the Società Italiana di Medicina Interna (Italian Society of Internal Medicine).

## RESULTS

### Participants

Of the 40 participants invited, there were 31 from 7 countries who represented 10 clinical and methodological specialties (Table). A complete roster is included in Table E1, available online at <http://www.annemergmed.com>.

### Conceptual Model

We acknowledged the differing perspectives of participants, whose clinical practices span multiple specialties and settings. To focus the discussions, we developed a conceptual model of the ED decisionmaking for syncope (Figure 1). Four critical questions were the focus of the discussion: (1) Is it syncope? (2) Is there a serious condition related to syncope identified in the ED? (3) If the cause for syncope is uncertain, what is the risk

**Table.** Participant characteristics.

Country	n	Percentage
Canada	4	13
Denmark	1	3
Germany	1	3
Italy	14	45
The Netherlands	3	10
United Kingdom	2	6
United States	6	20
<b>Specialty</b>		
Biostatistics	2	6
Cardiology	7	23
Economics	2	6
Emergency medicine	8	26
Geriatrics	1	3
Internal medicine	7	23
Neurology	1	3
Occupational medicine	1	3
Patient advocacy	1	3
Psychology	1	3

of a serious outcome? (4) For a given risk profile, what evaluations and functional restrictions are appropriate? Research agenda recommendations (Figure 2) are organized around these decision points.

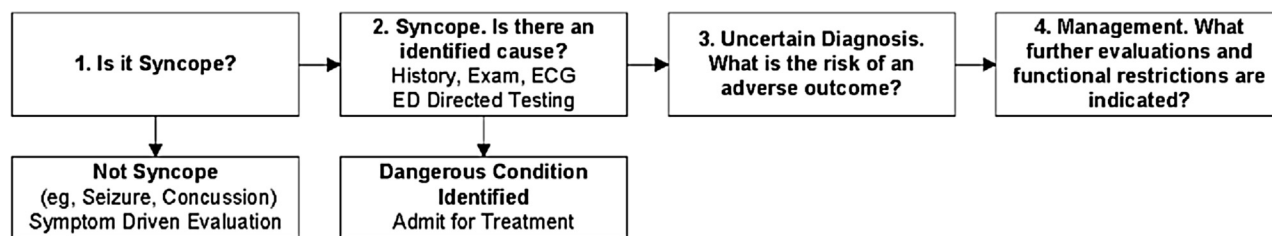
Subsequent evaluation and management after the initial ED encounter are aimed at refining a pathophysiologic explanation of the syncopal episode to guide further testing and management. Post-ED evaluation may also be invaluable for addressing patient quality of life concerns.<sup>42</sup> Although we addressed the transition from ED to post-ED care, specific recommendations for post-ED evaluation and management of syncope were beyond the scope of this meeting.

## RESEARCH AGENDA

### Is It Syncope?

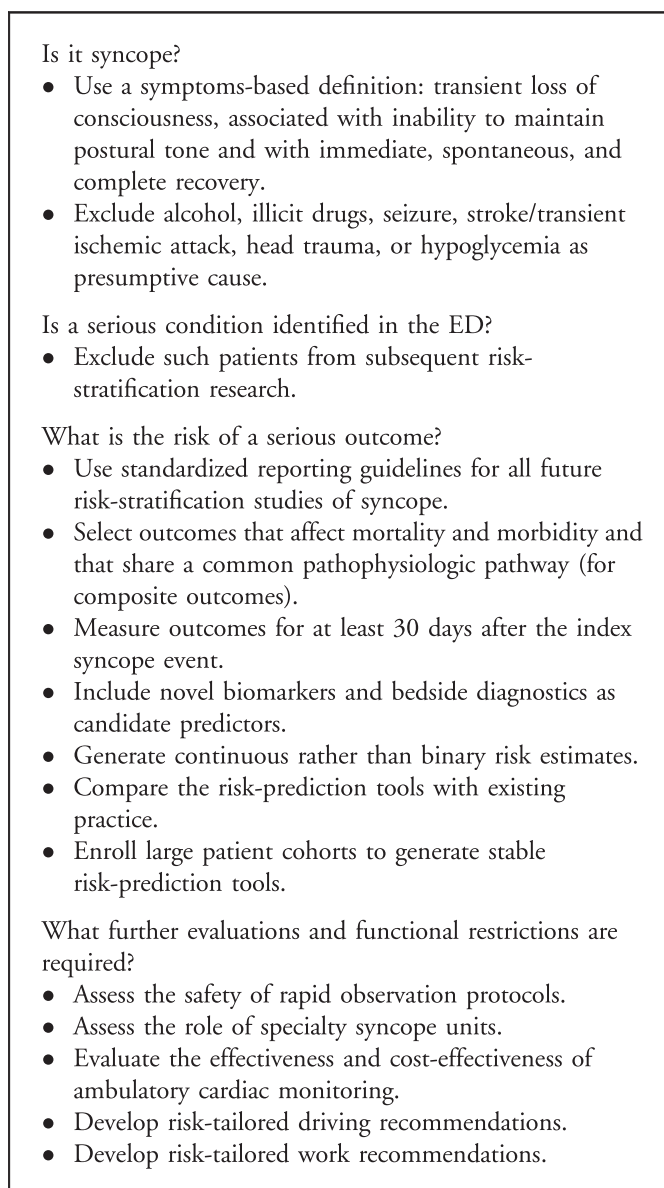
Professional society groups offer varying definitions of syncope,<sup>24,25,27,28</sup> and numerous variants exist in the research literature<sup>43,44</sup> (Table E2, available online at <http://www.annemergmed.com>). Standardizing the definition of “syncope” for future research is critical to the development of the field. To minimize conceptual and diagnostic confusion, the European Society of Cardiology defined syncope according to features of clinical presentation and pathophysiologic mechanism.<sup>25</sup> The European Society of Cardiology definition excludes conditions such as epilepsy and traumatic brain injury, and explicitly defines syncope as a loss of consciousness because of global cerebral hypoperfusion.

However, a definition of syncope that requires global cerebral hypoperfusion lacks a practical implementation that can be used in ED settings. Furthermore, the ability of ED clinicians to fully characterize a potential syncope event is often limited by poor patient recall, lack of witnesses, and time pressure. Even after hospital admission, nearly half of patients are discharged without a known cause of syncope.<sup>10</sup>



**Figure 1.** Conceptual model: ED management of syncope.

For the purpose of ED-based research, we endorse a pragmatic definition of syncope that excludes conditions caused by other plausible conditions and includes where possible specific syncopal conditions (Figure 2). We explicitly accept that this will involve



**Figure 2.** Research priorities.

some error, as is exemplified in the 27% sensitivity coding error for syncope in Danish hospitals.<sup>45</sup> This definition was developed through a previous expert-panel process,<sup>46</sup> is consistent with the intent of the European Society of Cardiology guidelines, and can be practically implemented in the ED. Several participants from the European Society of Cardiology consensus process<sup>25</sup> were present and supportive of this inclusive definition for this purpose.

We define syncope as a transient loss of consciousness, associated with inability to maintain the postural tone and with immediate spontaneous and complete recovery, associated with at least 1 of the following: (1) clinical features suggestive of specific forms of syncope (eg, vasovagal, orthostatic, cardiac); or (2) the absence of clinical features specific for another form of transient loss of consciousness such as epileptic seizure, hypoglycemia, or trauma. “Clinical features” indicates all the information obtained from the history, physical examination, and directed testing.<sup>47</sup>

The above definition of syncope permits inclusion of a presentation of vasovagal syncope if it has a specific associated cluster of features such as provoking factors and excludes a presentation with traumatic brain injury or epileptic convulsions as the cause of loss of consciousness. Patients without evident features of specific syncope causes, but also without other evident features of, for example, epilepsy or diabetic hypoglycemia, would also be included as having syncope.

### Is a Serious Condition Identified in the ED?

The initial ED evaluation relies on the triad of careful history taking, physical examination, and the 12-lead ECG.<sup>24,25,27,28</sup> Additional testing should be directed by the findings of this initial evaluation.<sup>48</sup> Nonselective use of other diagnostics, including laboratory tests, echocardiography, neurologic imaging tests, carotid ultrasonography, electroencephalography, and cardiac stress testing, among others, has very low diagnostic yield (<2%)<sup>10</sup> and should not be undertaken routinely.

The ED evaluation will reveal a serious causal clinical condition in a minority of patients. In one cohort of older adults, 10% received a final ED diagnosis of a clinically significant arrhythmia, severe anemia, myocardial infarction, pulmonary embolism, or stroke associated with the initial presentation of syncope.<sup>11</sup> Patients with an identified serious condition do not require further risk stratification; rather, they require appropriate management of the serious condition.

However, virtually all published risk-stratification studies have included patients who had a serious condition identified during the ED evaluation. From a clinical perspective, risk stratification is unnecessary if a dangerous diagnosis is already established. Inclusion of such patients in risk-stratification studies biases results toward the identification of “obvious” problems. For example, previous studies suggest that low hematocrit level was predictive of serious outcomes in syncope<sup>8,36</sup>; however, when patients with obvious gastrointestinal bleeding were excluded, hematocrit level was no longer associated with adverse events.<sup>11</sup>

ED syncope risk stratification research should exclude patients with serious conditions causing syncope that are identified in the ED (Figure 2).

### What Is the Risk of a Serious Outcome?

A major challenge in the evaluation of syncope is that a definitive cause is often in doubt. Most “diagnoses” are presumptive and cannot be confirmed by a criterion standard. For example, the finding of orthostatic hypotension cannot exclude an arrhythmic cause of syncope.<sup>49</sup> The ED clinician must estimate the risk of a serious event when the cause of syncope is in doubt, which in turn guides subsequent management and disposition. In the absence of explicit prediction tools, risk assessment is subjective and highly influenced by an individual physician’s experience and confounding historical features presented by the patient and witnesses.

Clinical decision aids can generate explicit estimates of risk. These may improve accuracy and consistency of risk stratification.<sup>50</sup> This strategy is particularly well suited for the ED setting, where providers must rapidly identify high-risk patients who present with undifferentiated symptoms.<sup>51</sup> As a result, there is international interest in improving diagnostic algorithms for syncope, and multiple risk-stratification tools have been published that attempt to identify low-risk patients who may be safely discharged.<sup>8,32-36,52</sup> External validation attempts have led to disappointing results,<sup>1,2,7,53</sup> and none of the published risk tools have been incorporated into routine practice.<sup>29,54</sup> We reviewed the limitations of the existing literature and recommend the following for future research on ED risk stratification for syncope (Figure 2):

- Use standardized data reporting guidelines. Existing studies demonstrate marked variability in defining study eligibility, outcomes, and predictors.<sup>43</sup> For example, previous studies have used different definitions of an abnormal ECG result.<sup>32,55,56</sup> A previous expert consensus effort developed a set of standardized data reporting elements.<sup>46</sup> Adherence to standardized reporting guidelines based on agreed-on data definitions will facilitate future literature review, data pooling, and meta-analysis.
- Select clinically important and coherent outcomes. Previous studies have used a wide range of outcomes, including various combinations of death, arrhythmia, nonarrhythmic cardiac disorders, noncardiac conditions, and measures of health

service use. Primary outcomes should be clinically important (ie, related to death or morbidity), and composite outcomes should be clinically coherent. For example, the factors that predict cardiac arrhythmia, pulmonary embolism, vertebrobasilar stroke, and occult gastrointestinal bleeding are likely to be very different.

- Measure 30-day outcomes. Previous investigators have measured outcomes ranging from 7 days to 1 year after the ED index visit. Ideally, the outcome time frame should maximize the likelihood that a serious outcome is related to the initial syncope episode and affects ED decisionmaking. Admittedly, the choice of time frame is somewhat arbitrary. In accordance with previous consensus panel work, we recommend the use of 30-day outcomes.<sup>46</sup>
- For predictors, published studies have focused on the triad of history, examination, and ECG findings. Emerging diagnostics may provide independent prognostic information. For example, pilot studies suggest that B-type (brain) natriuretic peptide, N-terminal pro-brain natriuretic peptide, and high-sensitivity troponin may be powerful predictors of serious outcomes after syncope.<sup>57-60</sup> Other emerging biomarkers such as copeptin, endothelin-1, arginine vasopressin, prealbumin, atrial natriuretic peptide, C-terminal proendothelin-1, proadrenomedullin, and adenosine<sup>61</sup> need further investigation.
- Generate continuous rather than binary risk estimates. Identification of “no-risk” patients has tremendous appeal in ED settings and has precedence, with clinical decision aids to exclude some types of traumatic injuries. However, it is unlikely that a “no-risk threshold” can be identified in patients for whom there is currently uncertainty about clinical management: older adults who have a nonzero risk of serious outcomes even in the absence of syncope. A continuous risk estimate allows greater flexibility. For example, it might help to identify low-risk patients for discharge and high-risk patients for admission.
- Compare risk-prediction tools with existing practice. Few studies compared explicit risk-stratification tools with physician judgment.<sup>55,62</sup> To complicate things further, decision aid performance will likely be context dependent and may safely reduce admissions in some settings but not in others.<sup>2</sup> Despite these challenges, comparison of a new instrument to existing clinical performance is essential to assess the potential benefit of the decision aid.
- Enroll large patient cohorts. A major challenge to researchers is the relatively low rate of significant clinical events after an unrevealing ED evaluation result ( $\approx 7\%$ ).<sup>11</sup> Previous derivation studies included 30 to 104 patients with significant outcomes, and small sample sizes may contribute to unstable models that do not generalize to other settings. Future studies require the enrollment of large cohorts to ensure reliable findings. Creation of a data registry that combines prospectively collected and standardized data may help address the sample size challenge.



## What Further Evaluations and Functional Restrictions Are Required?

The ED clinician's assessment of risk, whether generated subjectively or through an explicit risk score, must then determine the patient's disposition and plan for post-ED care. Most specialty society guidelines advocate the admission of "high-risk" patients and the discharge of "low-risk" ones.<sup>24-26</sup> Although this approach seems reasonable, there are several important limitations. First, the risk thresholds for "high" and "low" have never been defined, and risk tolerance is likely to vary by setting. For example, hospital admission rates for syncope range from 12% in some parts of Canada<sup>2</sup> to more than 80% in selected US academic centers.<sup>9</sup> Second, there is conflicting evidence about whether hospital admission improves outcomes after syncope.<sup>21,35</sup> Third, there is scant guidance for the management of patients who are at intermediate risk (ie, neither high or low risk) for serious outcomes.<sup>24</sup> Finally, there are limited data to guide recommendations for postdischarge driving and working.

We identified high research priorities to address these gaps (Figure 2). We recognize that clinical recommendations are conditional on risk assessment, and future research should carefully describe risk profiles of study populations. Also, randomized evaluation of health services interventions may not be feasible at the individual level. Alternative evaluation designs include randomized cluster trials, randomized registries, and evaluation of natural experiments (eg, pre-post intervention with control). Relevant outcomes include patient mortality and quality of life, health services use, and costs. Finally, we recognize that ED decisionmaking on these topics is most relevant for discharged patients; these issues will typically be addressed by inpatient physicians for admitted patients.

**ED observation protocols.** Two randomized trials demonstrate that a structured, ED-based observation protocol can reduce hospitalizations, length of stay, and costs without apparent effect on serious clinical events, quality of life, and patient satisfaction.<sup>38,63</sup> However, these studies enrolled fewer than 300 patients combined, and additional work is needed to definitively demonstrate the safety and diagnostic yield of such an approach.

**Specialty syncope unit.** Several European studies have assessed the value of multispecialty units that focus specifically on the evaluation of syncope. Such units may be hospital-based or outpatient clinics. Although some studies have demonstrated improved diagnostic rates and reduced resource use, these results have not been uniform.<sup>4,64-68</sup> Future research should focus on appropriate patient selection and safety of referral to such units.

**Ambulatory cardiac monitoring.** Technological advances have improved options for prolonged outpatient cardiac monitoring, some of which are real time or near real time. Shifting cardiac monitoring from inpatient to outpatient settings may reduce costs and improve diagnostic rates by increasing the total duration of monitoring.

**Driving recommendations.** Mandatory reporting requirements to motor vehicle agencies after an episode of

syncope vary significantly by country and locale. In a US cohort of patients who experienced syncope while driving, 1.1% experienced 12-month recurrent syncope while driving.<sup>69</sup> However, this study did not stratify risk by clinical characteristics or driving exposure. Additional studies should clarify the driving related risks for patients experiencing syncope and to the public.

**Work recommendations.** There are virtually no data to guide recommendations to resume work, particularly in high-risk occupations. In one European cohort, 6% reported syncope while at work. A history of syncope was associated with 4.6-fold greater risk of syncope at work; however, there was approximately 1 syncopal event at work for every 16 person-years of work for those patients who previously experienced syncope at work.<sup>70</sup> According to the Eurostat Health and Safety at Work in Europe report (Eurostat), most fatal accidents are classified as occurring after "loss of control," "slipping," "stumbling," and "falling."<sup>71</sup> All these conditions might be the consequence of an occult syncope, producing a sudden loss of consciousness and postural tone.<sup>72</sup> Future research should develop work recommendations tailored to clinical and occupational risk.

## LIMITATIONS

To our knowledge, this is the first organized effort to develop a syncope research agenda that spans specialties and countries. We acknowledge the following potential limitations.

First, participants represent a convenience sample and may not represent all syncope research experts. However, conference participants collectively have published multiple research articles on the topic and have contributed to the multiple professional society guidelines on the clinical management of syncope.

Second, we did not use formal qualitative research methods such as transcription and grounded theory analytic techniques. We believe this is mitigated by the face validity of our findings and the strength of consensus achieved for the recommendations.

Third, conference activities were endorsed by Italian medical societies but not by other non-Italian professional groups. Our participants are members of multiple emergency medicine, cardiovascular, and electrophysiology professional groups, but we did not seek endorsements from these societies before the conference meeting. In retrospect, we should have arranged for additional professional society endorsements.

## CONCLUSIONS

Syncope evaluation and management in the ED remains a vexing clinical challenge, and current practice is characterized by high costs, low diagnostic yield, and unclear clinical benefits. We convened a multispecialty group of syncope experts to identify the most pressing knowledge gaps and defined a high-priority research agenda.

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Please rank your priorities in addressing the problem of syncope risk stratification in the ED (0 less, 5 most).

New studies aimed at developing new clinical decision rules

New studies aimed at validating the existing clinical decision rules

Developing other risk-stratification tools

Developing neural networks

Assessing the utility of biomarkers

New studies focused on health services organization (for example, syncope units)

**Figure E1.** Preconference research priority questions.

**Table E1.** Conference participants.

Name	Academic Degree	Institution	Specialty	Country
Franca Barbic	MD	ICH, Rozzano	Occupational medicine	Italy
Daniel Beach	PhD	STARS	Patients association	UK
Nicolai Bodemer	PhD	Max Planck Institute, Berlin	Psychology	Germany
Ilaria Bossi	MD	Ospedale S. Anna, Como	Emergency medicine	Italy
Michele Brignole	MD	Ospedali del Tigullio, Lavagna	Cardiology	Italy
Ivo Casagrande	MD	Ospedale di Alessandria	Emergency medicine	Italy
Giovanni Casazza	PhD	Università degli Studi di Milano	Biostatistics	Italy
Giorgio Costantino	MD	Ospedale L. Sacco, Milano	Internal medicine	Italy
Franca Dipaola	MD	ICH, Rozzano	Internal medicine	Italy
Piergiorgio Duca	MD, PhD	Università degli Studi di Milano	Biostatistics	Italy
Greta Falavigna	PhD	CNR, Torino	Economics	Italy
Raffaello Furlan	MD	Università degli Studi di Milano, ICH, Rozzano	Internal medicine	Italy
Andrew Kohn	MD	University of British Columbia	Cardiology	Canada
Roberto Ippoliti	PhD	Ospedale di Alessandria	Economics	Italy
Daniel McDermott	MD	UCSF, School of Medicine	Emergency medicine	USA
Nicola Montano	MD, PhD	Università degli Studi di Milano	Internal medicine	Italy
Brian Olshansky	MD	University of Iowa Medical Center	Cardiology	USA
James Quinn	MD	Stanford University	Emergency medicine	USA
Satish R. Raj	MD, MSCI	Vanderbilt University	Cardiology	USA
Matthew Reed	MD	Royal Infirmary of Edinburgh	Emergency medicine	UK
Martin H. Ruwald	MD, PhD	Gentofte Hospital	Cardiology	Denmark
Robert S. Sheldon	MD, PhD	University of Calgary	Cardiology	Canada
Win-Kuang Shen	MD	Mayo Clinic	Cardiology	USA
Monica Solbiati	MD	Università degli Studi di Milano	Internal medicine	Italy
Ian Stiell	MD	University of Ottawa	Emergency medicine	Canada
Benjamin Sun	MD	Oregon Health and Science University	Emergency medicine	USA
Venkatesh Thiruganasambandamoorthy	MBBS, MSc	University of Ottawa	Emergency Medicine	Canada
Andrea Ungar	MD	Ospedale Careggi, Firenze	Geriatrics	Italy
Gert van Dijk	MD, PhD	Leiden University Medical Centre	Neurology	The Netherlands
Nynke van Dijk	MD, PhD	Academic Medical Center-University of Amsterdam	Internal Medicine	The Netherlands
Wouter Wieling	MD	Academic Medical Center-University of Amsterdam	Internal Medicine	The Netherlands



**Table E2.** Professional society definitions of syncope.

Organization	Definition
American Heart Association <sup>1</sup>	Transient loss of consciousness
American College of Emergency Physicians <sup>2</sup>	Brief loss of consciousness with an inability to maintain postural tone that spontaneously and completely resolves without medical intervention
American College of Physicians <sup>3</sup>	Transient loss of consciousness accompanied by loss of postural tone
European Society of Cardiology <sup>4</sup>	Transient loss of consciousness because of transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous recovery

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